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Flow-limited and Reverse-triggered Ventilator Dyssynchrony Are Associated with Increased Tidal and Dynamic Transpulmonary Pressure

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Abstract

Objective: Ventilator dyssynchrony may be associated with increased delivered tidal volumes and dynamic transpulmonary pressure, surrogate markers of lung stress and strain, despite low tidal volume ventilation. However, it is unknown which types of ventilator dyssynchrony are most likely to increase these metrics or if specific ventilation or sedation strategies can mitigate this potential.

Design: A prospective cohort analysis to delineate the association between ten types of breaths and delivered tidal volume (V_t), dynamic transpulmonary pressure ($\Delta P_{L,dyn}$), and transpulmonary mechanical energy

Setting: Patients admitted to the Medical ICU.

Patients: Over 580,000 breaths from thirty-five patients with ARDS or ARDS risk factors.

Interventions: None

Measurements: Patients received continuous esophageal manometry. Ventilator dyssynchrony was identified using a machine learning algorithm. Mixed-effect models predicted V_t, $\Delta P_{L,dyn}$, and transpulmonary mechanical energy for each type of ventilator dyssynchrony while controlling for repeated measures. Finally, we described how tidal volume, PEEP, and sedation (Richmond Agitation and Sedation Score) strategies modify ventilator dyssynchrony's association with these surrogate markers of lung stress and strain.

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Main Results: Double-triggered breaths were associated with the most significant increase in V_t, $\Delta P_{L,dyn}$, and transpulmonary mechanical energy. However, flow-limited, early reverse-triggered, and early ventilator-terminated breaths were also associated with significant increases in V_t, $\Delta P_{L,dyn,}$ and energy. The potential of a ventilator dyssynchrony type to increase V_t, $\Delta P_{L,dyn,}$ or energy clustered similarly. Increasing set tidal volume may be associated with a disproportionate increase in high-volume and high-energy ventilation from double-triggered breaths, but PEEP and sedation do not clinically modify the interaction between ventilator dyssynchrony and surrogate markers of lung stress and strain.

Conclusion: Double-triggered, flow-limited, early reverse-triggered, and early ventilator-terminated breaths are associated with increases in V_t, $\Delta P_{L,dyn,}$ and energy. As flow-limited breaths are more than twice as common as double-triggered breaths, further work is needed to determine the interaction of ventilator dyssynchrony frequency to cause clinically meaningful changes in patient outcomes.

Keywords

Acute Respiratory Distress Syndrome; Ventilator-Induced Lung Injury; Mechanical Ventilators; Manometry; Humans

Introduction

Mechanical ventilation with large tidal volume, high pressure, or repeated alveolar collapse causes ventilator-induced lung injury (VILI).(1) Low tidal volume ventilation (LTVV) can reduce VILI and improve patient outcomes but does not eliminate the development of VILI.(2–5) Ventilator dyssynchrony is defined as the inappropriate timing and delivery of a breath in response to patient effort and respiratory muscle activation.(6) There are multiple types of ventilator dyssynchrony (Figure A1).(7–12) Ventilator dyssynchrony causes lung injury through multiple mechanisms, including volutrauma and barotrauma. For instance, double-triggered breaths are associated with increased delivered tidal volumes ($V_{t,d}$), while early reverse-triggered breaths are associated with increased transpulmonary pressures.(13–16) While double-triggered breaths are an obvious source of excessive tidal volume, it remains unknown if more common types of ventilator dyssynchrony are associated with increases in tidal volume, dynamic transpulmonary pressure, or mechanical energy and thereby be deleterious to the lung.(17)

Tidal volume is a surrogate marker for lung strain. Depending on the ventilator mode, it is generated both from the ventilator settings and patient effort. Esophageal manometry is a tool to quantify patient effort and the potential risk of barotrauma.(18, 19) Specifically, esophageal manometry allows the measurement of dynamic transpulmonary pressure ($\Delta P_{L,dyn}$), which measures the stress applied to the lung parenchyma from the combination of the ventilator and patient effort.(20, 21) Transpulmonary mechanical energy is a novel risk factor of VILI that may be a unifying measure to quantify the risk of VILI regardless of the mode of injury.(22–28) Consequently, transpulmonary mechanical energy may offer unique insights to determine which types of ventilator dyssynchrony are most harmful to the lung compared to measures of strain (V_t) or stress ($\Delta P_{L,dyn}$) alone.

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Whether specific ventilator strategies modify the association between ventilator dyssynchrony and tidal volume, $\Delta P_{L,dyn}$, or energy is unknown. Low set tidal volume ($V_{t,s}$) ventilation and optimal positive end-expiratory pressure (PEEP) are two possible ventilation strategies that reduce VILI in ARDS and may alter the association between ventilator dyssynchrony and surrogate markers of lung strain and stress.(3, 29, 30) Similarly, sedation strategies have been studied to minimize VILI by reducing the work of breathing.(15, 31–33) However, whether a tidal volume, PEEP, or sedation strategy modifies the association between ventilator dyssynchrony and intermediate markers of VILI remains unknown.

Consequently, we first sought to determine which ventilator dyssynchrony types are associated with increased delivered tidal volume, dynamic transpulmonary pressure, and transpulmonary mechanical energy. Second, we determined the consistency of this ranking over these three metrics. Transpulmonary pressure and transpulmonary mechanical energy require additional invasive monitoring to measure, and determining if these measures add additional information to determine which types of ventilator dyssynchrony are deleterious is essential for the clinical monitoring of ventilator dyssynchrony. Finally, we determined whether $V_{t,s}$, PEEP, and the degree of sedation, measured by the Richmond Agitation and Sedation Score (RASS), modified the effect of the association between ventilator dyssynchrony and V_t, $\Delta P_{L,dyn,}$ and mechanical energy.

Materials and Methods

We performed a prospective cohort study of patients admitted to the University of Colorado Medical, Surgical, Neurosurgical, and COVID ICUs with ARDS defined by the Berlin definition or risk factors for ARDS (See Appendix for additional inclusion and exclusion criteria).(34) Patient characteristics were extracted from the electronic medical record. These included age, gender, race, etiology of ARDS, the initial PaO_2 to FiO_2 ratio (P:F), and RASS score (recorded every 4 hours). Informed consent was obtained from the patient's identified proxy decision-maker. The project was approved by the University of Colorado Multiple Institutional Review Board (COMIRB, #18-1433, Approved July 18, 2018, The Detection, Quantification, and Management of Ventilator Dyssynchrony). Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (COMIRB) and with the Helsinki Declaration of 1975.

Continuous ventilator data were collected using a laptop connected to the ventilator using Hamilton DataLogger software (Hamilton, v5.0, 2011) to obtain time-stamped measures of airway pressure, flow, volume, and esophageal pressure. An esophageal balloon (CooperSurgical; Truball, CT) was inserted at the time of enrollment if not already placed by the primary team as part of clinical care. The balloon occlusion test confirmed proper placement.(35, 36) Airway pressure, flow, volume, and esophageal pressure were measured every 32 milliseconds. Ventilator data were collected for 48 hours from the time of balloon placement.

Our machine learning (ML) pathway for ventilator dyssynchrony identification is detailed previously.(15) We then delineated the association between each ventilator dyssynchrony type and $V_{t,d}$, $\Delta P_{L,dyn}$, and transpulmonary mechanical energy. We calculated three

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separate hierarchical linear mixed-effect models to predict $V_{t,d}$, $\Delta P_{L,dyn}$, and transpulmonary mechanical energy, respectively (see Appendix, Figure A5 for a directed acyclic graph of the pathways studied). Each type of ventilatory dyssynchrony was included as a fixed-effect in the model; normal passive breaths were the reference group of each model. Finally, each patient's data was grouped into 250-breath, time-ordered intervals to adjust for changing pulmonary dynamics over time and ensure stationarity. Each 250-breath group was nested by Patient ID as a random intercept to correct for repeated measures by patient.(37) Each model was fit to a normally distributed outcome variable using the identity link.

We also determined if $V_{t,s}$, PEEP, or RASS were effect modifiers for the association between the type of ventilator dyssynchrony and $V_{t,d}$, $\Delta P_{L,dyn}$, and transpulmonary mechanical energy, respectively. The above modifiers were each included in separate mixed-effect models as an interaction term with each type of ventilator dyssynchrony. Interactions were determined significant if both the variable and its interaction were significant. The significance of all p-values was adjusted for multiple tests using the Bonferroni correction. Consequently, a p-value of less than 0.0005 was deemed statistically significant. Statistical analysis was completed in Julia v1.8.4.(38)

Results

A total of 323 patients with ARDS or ARDS risk factors receiving mechanical ventilation on a Hamilton G5 were identified. Of these, 253 patients met the exclusion criteria. Of the remaining 70 patients, 56 patients had esophageal balloons placed for the study, and 14 patients were enrolled after esophageal balloon placement during clinical care. To ensure accurate P_{es} results, patients without suitable esophageal balloon signals were eliminated after a manual review of P_{es}, yielding a subset of 35 patients and a total of 578,936 breaths for analysis (Figure 1, see Appendix for additional details). Demographic data is reported in Table 1. Adaptive pressure ventilation-controlled mechanical ventilation (APVCMV) mode was the predominant ventilation mode (see Appendix for a description of APVCMV).(39)

Ventilator dyssynchrony was observed in 29.1% of breaths (Table 2). Late reverse triggered, reverse triggered double triggered, mild flow limited, and severe flow limited, respectively, accounted for 6.4%, 4.1%, 8.8%, and 4.6% of all breaths. On average, all breaths, regardless of type, were associated with a mean $V_{t,d}$ of 6.9±2.1 ml/kg PBW, a mean $\Delta P_{L,dyn}$ 13.5±3.8 cmH_2O, and a mean transpulmonary mechanical energy of 354±185 mJ.

Patient-triggered and reverse-triggered double-triggered breaths were associated with a delivered tidal volume of 14.5 and 12.7 ml/kg PBW compared to 6.1 ml/kg PBW in normal, passive breaths (an 8.34 [8.3, 8.38] and 6.59 [6.57, 6.61] ml/kg increase in V_t, respectively, mean [95% CI]). Similarly, severe flow limited, early reverse triggered, mild flow limited, and early ventilator terminated breaths were associated with a 7.9, 7.3, 7.3, and 7.0 ml/kg PBW delivered tidal volume, respectively, compared to 6.1 ml/kg PBW in normal, passive breaths (a 1.82 [1.8, 1.84], 1.20 [0.93, 1.47], 1.17 [1.15, 1.19] and 0.85 [0.83, 0.87] ml/kg increase in V_t, respectively, Figure 2). All other types of ventilator dyssynchrony were associated with a small but statistically significant increase in delivered tidal volume compared to normal, passive breaths (Appendix: Table A1). Moreover, patient-triggered

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double-triggered, reverse-triggered double-triggered, severe flow-limited, mild flow-limited, early reverse-triggered, early ventilator terminated breaths were associated with a $\Delta P_{L,dyn}$ of 18.3, 18.1, 15.5, 15.1, 14.9, and 14.7, respectively, compared to 13.4 cmH_2O in normal, passive breaths (a 4.9 [4.8, 5.0], 4.8 [4.8, 4.8], 2.1 [2.1, 2.1], 1.8 [1.8, 1.8], 1.5 [1.4, 1.6], and 1.3 [1.2, 1.4] cmH_2O increase in $\Delta P_{L,dyn}$ respectively, Figure 3, Appendix: Table A2). Normal, spontaneous breaths were associated with a 2.8 [2.8, 2.8] cmH_2O increase in $\Delta P_{L,dyn}$ (16.2 vs. 13.4 cmH_2O) compared to normal, passive breaths. Similar trends were observed for transpulmonary mechanical energy and ventilator dyssynchrony types ordered similarly between $V_{t,d}$, $\Delta P_{L,dyn}$, and transpulmonary mechanical energy, as detailed in the Appendix.

Finally, we focused on the four breath types with the strongest association with surrogate markers of lung stress and strain to investigate the effect modification of set tidal volume, PEEP, and RASS score on surrogate markers of lung stress and strain. Set tidal volume was positively associated as a significant interaction term between patient-triggered double-triggered, reverse-triggered double-triggered, severe flow-limited, mild flow-limited, and surrogate markers of stress and strain (Table A4). The PEEP and RASS interaction terms were statistically significant, but much smaller in magnitude. A detailed discussion is in the appendix (see Table A5 and A6).

Discussion

We delineated the association between ten types of breaths and delivered tidal volume, $\Delta P_{L,dyn}$, and transpulmonary mechanical energy. As anticipated, double-triggered breaths (both patient-triggered and reverse-triggered) showed an expected and large increase in V_t, $\Delta P_{L,dyn}$, and transpulmonary mechanical energy. However, we demonstrated that other types of ventilator dyssynchrony were also associated with increase stress and strain. Flow-limited, early ventilator terminated, and early reverse-triggered breaths showed clinically significant increases in V_t, $\Delta P_{L,dyn}$, and transpulmonary mechanical energy, suggesting that these ventilator dyssynchrony types. Moreover, rankings were consistent across V_t, $\Delta P_{L,dyn}$, and transpulmonary mechanical energy suggesting these findings are robust, and advanced monitoring with an esophageal balloon may not be necessary to identify injurious ventilator dyssynchrony. Finally, neither set V_t, PEEP, nor RASS score showed a consistent statistical interaction altering the association between surrogate markers of lung stress and strain and all types of ventilator dyssynchrony, suggesting there is no simple ventilation or sedation strategy to minimize the stress and strain associated across all ventilator dyssynchrony types.

This work is important for four reasons. First, and most importantly, we can now expand the different types of ventilator dyssynchrony that potentially increase surrogate markers of lung stress and strain, as quantified by changes in $V_{t,d}$, and $\Delta P_{L,dyn}$. In addition to double-triggered breaths, we highlight that flow-limited, early reverse-triggered, and early ventilator-terminated breaths are associated with increases in surrogate markers of lung stress and strain, which has not previously been described. Flow-limited breaths accounted for 13.4% of all breaths, suggesting a frequent potential source of stress and strain. While the magnitude of the change in V_t, $\Delta P_{L,dyn}$, and transpulmonary mechanical energy associated with flow-limited breaths is moderate, these types of ventilator dyssynchrony

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are more than 2.5 times more frequent in our dataset. Finally, late reverse-triggered, late ventilator terminated, and ineffective triggered breaths are not clinically different from normal, passive breaths and, therefore, unlikely to be associated with a meaningful increase in lung stress and strain compared to normal passive breaths.

Second, these data build on the work of others to quantify the potential for increased lung stress and strain. Several authors have previously demonstrated that double-triggered breaths were associated with a nearly two-fold increase in tidal volumes, while early reverse-triggered breaths were associated with a more mild increase in V_t.(8, 13–15) Similarly, we build on the work of Kassis, et al and confirmed that transpulmonary pressure was increased in early reverse triggered but not late reverse triggered breaths.(8) We add to this prior body of work by characterizing additional types of ventilator dyssynchrony - namely mild flow-limited, severe flow-limited, early ventilator-terminated, late ventilator-terminated, and ineffective triggered breaths. Importantly, flow-limited breaths are associated with increases in $V_{t,d}$, $\Delta P_{L,dyn}$, and mechanical energy. Moreover, the degree of p_{aw} coving (Figure A1) correlates with an increase in delivered V_t and $\Delta P_{L,dyn}$, suggesting that the potential of flow-limited breaths to increases in $V_{t,d}$ and $\Delta P_{L,dyn}$, is variable and proportional to patient effort. Thus, there is heterogeneity within a given ventilator dyssynchrony type to propagate VILI. Additionally, we noted that early reverse-triggered and early ventilator-terminated breaths also are associated with similar increases in $\Delta P_{L,dyn}$. This is consistent with the mechanism driving both dyssynchronies - diaphragmatic contraction during end-inspiration and into expiration.

Third, we confirmed that measuring $V_{t,d}$, and $\Delta P_{L,dyn}$, and transpulmonary mechanical energy led to a similar ordering of the potential for ventilator dyssynchrony types to propagate VILI. Despite lacking collinearity, these measures generate similar rankings of $V_{t,d}$, $\Delta P_{L,dyn}$, and transpulmonary, suggesting that utilizing the easier-to-measure V_t may be sufficient to predict VILI in future studies. We calculated the energy through the entire respiratory cycle as the time integral of flow times transpulmonary pressure. Our approach is different from the method proposed by Gattinoni, who used point estimates of inspiratory mechanics to estimate the inspiratory power, but more similar to the more accurate derivation described by Trinkle (Appendix, Figure A4).(22, 28) We included the expiratory energy because late reverse triggered, early ventilator terminated, late ventilator terminated, ineffective, and double-triggered breaths have many changes in either transpulmonary pressure or flow waveforms that occur during the expiratory phase of the breath, which would not be accounted for by Gattinoni's or Trinkle's approach. This decision, though, came at the cost of not being able to directly compare our energy calculations to prior studies that have associated an inspiratory power threshold with a propensity for lung injury.(23–27)

Finally, we sought to assess if low tidal volume, high PEEP, or deep sedation would blunt the associations between ventilator dyssynchrony and V_t, $\Delta P_{L,dyn}$, or transpulmonary mechanical energy. For instance, very low tidal volume ventilation may worsen air hunger, thereby increasing the work of breathing and amplifying the deleterious transpulmonary pressures generated by ventilator dyssynchrony. Alternatively, increased PEEP could recruit more alveoli, thus reducing the work of breathing and decreasing the transpulmonary

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pressure or high volumes associated with different ventilator dyssynchrony types. The effect modification of set $V_{t,s}$ on the delivered tidal volume ($V_{t,d}$) is easiest to understand. If ventilator dyssynchrony had no interaction, one would expect that for each 1 ml/kg PBW increase in set V_t, a 1ml/kg increase would be seen in delivered V_t. Indeed, this was observed for both passive and spontaneous normal breaths. However, we observed that an increase in set tidal volume was associated with a 2–3-fold increase in the delivered tidal volume from double-triggered breaths compared to normal, passive breaths. While a near doubling of V_t would be expected, given that a double-triggered breath has two inspiratory periods without complete exhalation, we observed an even larger change in V_t. It is a reminder that increasing the set tidal volume from 6 to 8 ml/kg PBW, as allowed in the original ARMA protocol, could result in a delivered V_t during double-triggered breaths of up to 16-24 ml/kg PBW for double-trigger dyssynchronies.(3, 40) Similar associations were observed using mechanical energy. Conversely, the transpulmonary pressure associated with flow-limited breaths may be reduced with increased set V_t. Higher V_t may better match patient volume needs, reducing patient effort, and thus flow needs, and finally decreasing $\Delta P_{L,dyn}$. The effects of PEEP and RASS on these measures were not clinically significant. We acknowledge that the complex interaction between pressure, volume, patient effort, and ventilator settings are easily confounded in this observational analysis. For example, the decrease in $\Delta P_{L,dyn}$ with increasing set V_t observed in reverse-triggered double-triggered and patient-triggered double-triggered breaths may be from the ventilator pressure limiting at higher volumes rather than ventilator dyssynchrony independently affecting $\Delta P_{L,dyn}$. Thus, these data suggest that ventilator and sedation strategies may not affect ventilator dyssynchrony's potential to increase surrogate markers of stress and strain. However, sedation strategies do affect the frequency of ventilator dyssynchrony. Future intervention may need to focus on decreasing ventilator dyssynchrony instead of altering its potential to increase stress and strain.(15)

This study has multiple important limitations. First, we can only assess associations between variables in this prospective cohort study. Unmeasured confounding between ventilator settings or treatment decisions, patient physiology, and ventilator dyssynchrony types may mask these associations. This may be particularly present in our mediation analysis. For instance, lower tidal volume, higher PEEP, and deeper sedation are more often utilized in patients with worse ARDS and poor lung compliance, directly impacting our selected outcome variables. We controlled for these concerns including each patient nested by time as random-effect in our models, but unmeasured confounding may remain. Secondly, while we studied over 500,000 breaths, our sample size of thirty-five patients was small. Because ventilator dyssynchrony can vary between patients, a larger sample size may improve the generalizability of our conclusions. However, enrolling more patients was limited by the difficulty of obtaining proxy consent for the esophageal balloons needed to measure our outcome variables. Third, over half of our recorded breaths had adequate esophageal waveform data, but a substantial number of breaths and patients were excluded because of incomplete data. However, general patient characteristics were not statistically different between patients with complete and incomplete data. Fourth, esophageal balloons deflate over time, dampening their signal and biasing transpulmonary calculations to that of the measured airway pressure. This dampening would reduce the magnitude of any findings

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and bias our results toward dynamic airway pressure, reducing the effect of diaphragmatic contraction. We manually reviewed all P_{es} tracings to minimize this loss signal. Similarly, esophageal spasms and patient movement may generate spurious P_{es} signals, but these are typically brief and random compared to ventilator dyssynchrony and affect few breaths. Fifth, this is a single-center study, where most patients receive the proprietary Hamilton APVCMV mode of ventilation, further limiting generalizability.

Conclusion

Ventilator dyssynchrony is frequent, with reverse triggered and flow-limited breaths each accounting for most of this cohort's witnessed ventilator dyssynchrony. Reverse-triggered double-triggered, patient-triggered double-triggered, mild flow-limited, severe flow-limited, early ventilator terminated, and early reverse-triggered are all associated with increased V_T, $\Delta P_{L,dyn,}$ and mechanical energy. These data suggest that reverse-triggered, double-triggered breaths, and flow-limited breaths have the strongest potential to increase surrogate markers of lung stress and strain. However, given that each type of ventilator dyssynchrony occurs at different frequencies in different patients, it is possible that a more common type of ventilator dyssynchrony (i.e.: flow-limited), despite having a smaller by-breath indicator of increased stress or strain, may cause more injury to the lung over time. Consequently, more research is needed to understand the interplay between the type and frequency of ventilator dyssynchrony, the interaction with the degree of lung injury, the ability of ventilator dyssynchrony to worsen lung injury in the short term, and interventions required to improve patient outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Copyright Form Disclosure:

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References

1. Webb HH, Tierney DF: Experimental Pulmonary Edema Due to Intermittent Positive Pressure Ventilation with High Inflation Pressures. Protection by Positive End-Expiratory Pressure. Am Rev Respir Dis 1974; 110:556–65 [PubMed: 4611290]
2. Futier E, Constantin J-M, Paugam-Burtz C, et al. : A Trial of Intraoperative Low-Tidal-Volume Ventilation in Abdominal Surgery. N Engl J Med 2013; 369:428–37 [PubMed: 23902482]
3. Brower RG, Lanken PN, Macintyre N, et al. : Higher Versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome. N Engl J Med 2004; 351:327–36 [PubMed: 15269312]
4. Guay J, Ochroch EA: Intraoperative Use of Low Volume Ventilation to Decrease Postoperative Mortality, Mechanical Ventilation, Lengths of Stay and Lung Injury in Patients Without Acute Lung Injury. Cochrane Database Syst Rev Online 2015; 12:CD011151

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5. Determann RM, Royakkers A, Wolthuis EK, et al. : Ventilation with Lower Tidal Volumes as Compared with Conventional Tidal Volumes for Patients Without Acute Lung Injury: A Preventive Randomized Controlled Trial. Crit Care 2010; 14:R1 [PubMed: 20055989]
6. Gilstrap D, Davies J: Patient-Ventilator Interactions. Clin Chest Med 2016; 37:669–681 [PubMed: 27842747]
7. Branson RD, Blakeman TC, Robinson BR: Asynchrony and dyspnea. Respir Care 2013; 58:973–89 [PubMed: 23709195]
8. Baedorf Kassis E, Su HK, Graham AR, et al. : Reverse Trigger Phenotypes in Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2021; 203:67–77 [PubMed: 32809842]
9. Su HK, Loring SH, Talmor D, et al. : Reverse triggering with breath stacking during mechanical ventilation results in large tidal volumes and transpulmonary pressure swings. Intensive Care Med 2019; 45:1161–1162 [PubMed: 30923835]
10. Akoumianaki E, Lyazidi A, Rey N, et al. : Mechanical Ventilation-Induced Reverse-Triggered Breaths: A Frequently Unrecognized Form of Neuromechanical Coupling. Chest 2013; 143:927–938 [PubMed: 23187649]
11. Murias G, Lucangelo U, Blanch L: Patient-ventilator asynchrony. Curr Opin Crit Care 2016; 22:53–9 [PubMed: 26627539]
12. Delisle S, Charbonney E, Albert M, et al. : Patient-ventilator asynchrony due to reverse triggering occurring in brain-dead patients: Clinical implications and physiological meaning. Am J Respir Crit Care Med 2016; 194:1166–1168 [PubMed: 27797612]
13. Pohlman MC, Mccallister KE, Schweickert WD, et al. : Excessive Tidal Volume from Breath Stacking During Lung-Protective Ventilation for Acute Lung Injury. Crit Care Med 2008; 36:3019–23 [PubMed: 18824913]
14. Beitler JR, Sands SA, Loring SH, et al. : Quantifying Unintended Exposure to High Tidal Volumes from Breath Stacking Dyssynchrony in ARDS: The Breathe Criteria. Intensive Care Med 2016; 42:1427–36 [PubMed: 27342819]
15. Sottile PD, Albers D, Higgins C, et al. : The Association Between Ventilator Dyssynchrony, Delivered Tidal Volume, and Sedation Using a Novel Automated Ventilator Dyssynchrony Detection Algorithm. Crit Care Med 2018; 46:e151–e157 [PubMed: 29337804]
16. Pham T, Montanya J, Telias I, et al. : Automated detection and quantification of reverse triggering effort under mechanical ventilation. Crit Care Lond Engl 2021; 25:60
17. Damiani LF, Bruhn A, Retamal J, et al. : Patient-ventilator dyssynchronies: Are they all the same? A clinical classification to guide actions. J Crit Care 2020; 60:50–57 [PubMed: 32739760]
18. Akoumianaki E, Maggiore SM, Valenza F, et al. : The Application of Esophageal Pressure Measurement in Patients with Respiratory Failure. Am J Respir Crit Care Med 2014; 189:520–531 [PubMed: 24467647]
19. Talmor DS, Fessler HE: Are esophageal pressure measurements important in clinical decision-making in mechanically ventilated patients? Respir Care 2010; 55:162–72; discussion 172-4 [PubMed: 20105342]
20. Chiumello D, Carlesso E, Brioni M, et al. : Airway Driving Pressure and Lung Stress in ARDS Patients. Crit Care 2016; 20:276 [PubMed: 27545828]
21. Chiumello D, Carlesso E, Cadringher P, et al. : Lung Stress and Strain During Mechanical Ventilation for Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2008; 178:346–55 [PubMed: 18451319]
22. Gattinoni L, Tonetti T, Cressoni M, et al. : Ventilator-Related Causes of Lung Injury: The Mechanical Power. Intensive Care Med 2016; 42:1567–75 [PubMed: 27620287]
23. Cressoni M, Gotti M, Chiurazzi C, et al. : Mechanical Power and Development of Ventilator-Induced Lung Injury. Anesthesiology 2016; 124:1100–8 [PubMed: 26872367]
24. Serpa Neto A, Deliberato RO, Johnson AEW, et al. : Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts. Intensive Care Med 2018; 44:1914–1922 [PubMed: 30291378]
25. Parhar KKS, Zjadewicz K, Soo A, et al. : Epidemiology, Mechanical Power, and 3-Year Outcomes in Acute Respiratory Distress Syndrome Patients Using Standardized Screening. An Observational Cohort Study. Ann Am Thorac Soc 2019; 16:1263–1272 [PubMed: 31247145]

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26. Tonetti T, Vasques F, Rapetti F, et al. : Driving pressure and mechanical power: new targets for VILI prevention. Ann Transl Med 2017; 5:286 [PubMed: 28828361]
27. Dianti J, Matelski J, Tisminetzky M, et al. : Comparing the Effects of Tidal Volume, Driving Pressure, and Mechanical Power on Mortality in Trials of Lung-Protective Mechanical Ventilation. Respir Care 2021; 66:221–227 [PubMed: 32843513]
28. Trinkle CA, Broaddus RN, Sturgill JL, et al. : Simple, accurate calculation of mechanical power in pressure controlled ventilation (PCV). Intensive Care Med Exp 2022; 10:22 [PubMed: 35644896]
29. Cavalcanti AB, Suzumura ÉA, Laranjeira LN, et al. : Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (peep) Vs Low Peep on Mortality in Patients with Acute Respiratory Distress Syndrome - a Randomized Clinical Trial. JAMA - J Am Med Assoc 2017; 318
30. Fish E, Novack V, Banner-Goodspeed VM, et al. : The Esophageal Pressure-Guided Ventilation 2 (epvent2) Trial Protocol: A Multicentre, Randomised Clinical Trial of Mechanical Ventilation Guided by Transpulmonary Pressure. BMJ Open 2014; 4:e006356
31. Chanques G, Kress JP, Pohlman A, et al. : Impact of ventilator adjustment and sedation-analgesia practices on severe asynchrony in patients ventilated in assist-control mode. Crit Care Med 2013; 41:2177–87 [PubMed: 23782972]
32. Papazian L, Forel JM, Gacouin A, et al. : Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome. N Engl J Med 2010; 363:1107–16 [PubMed: 20843245]
33. PETAL Clinical Trials Network: Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome. N Engl J Med 2019; 380:1997–2008 [PubMed: 31112383]
34. Force ADT, Ranieri VM, Rubenfeld GD, et al. : Acute Respiratory Distress Syndrome: The Berlin Definition. JAMA 2012; 307:2526–33 [PubMed: 22797452]
35. Mojoli F, Iotti GA, Torriglia F, et al. : In vivo calibration of esophageal pressure in the mechanically ventilated patient makes measurements reliable. Crit Care 2016; 20:98 [PubMed: 27063290]
36. Chiumello D, Consonni D, Coppola S, et al. : The Occlusion Tests and End-Expiratory Esophageal Pressure: Measurements and Comparison in Controlled and Assisted Ventilation [Internet]. Ann Intensive Care 2016; 6[cited 2020 Jun 17] Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4751101/ [PubMed: 26762504]
37. West BT, Welch KB, Gałecki AT, et al.: Linear mixed models: a practical guide using statistical software. Second edition. Boca Raton: CRC Press, Taylor & Francis Group; 2015.
38. Bezanson J, Edelman AE, Karpinski S, et al. : Julia: A fresh approach to numerical computing. SIAM Rev 2017; 59:65–98
39. Chatburn RL, Mireles-Cabodevila E: Closed-Loop Control of Mechanical Ventilation: Description and Classification of Targeting Schemes. Respir Care 2011; 56:85–102 [PubMed: 21235841]
40. Malhotra A: Low-tidal-volume ventilation in the acute respiratory distress syndrome. N Engl J Med 2007; 357:1113–20 [PubMed: 17855672]

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Key Points:

Question:

To determine which types of ventilator dyssynchrony are most associated with increases in surrogate markers of lung stress and strain.

Findings:

In a prospective, observational study, we determined that double-triggered, flow-limited, early reverse-triggered, and early ventilator-terminated breaths were associated with significant increases in tidal volume, dynamic transpulmonary driving pressure, and transpulmonary mechanical energy.

Meaning:

While double-triggered breaths are an obvious source of high tidal volumes, additional types of dyssynchrony – namely flow-limited, early reverse-triggered, and early ventilator-terminated are associated with increases in V_t, $\Delta P_{L,dyn,}$ and mechanical energy.

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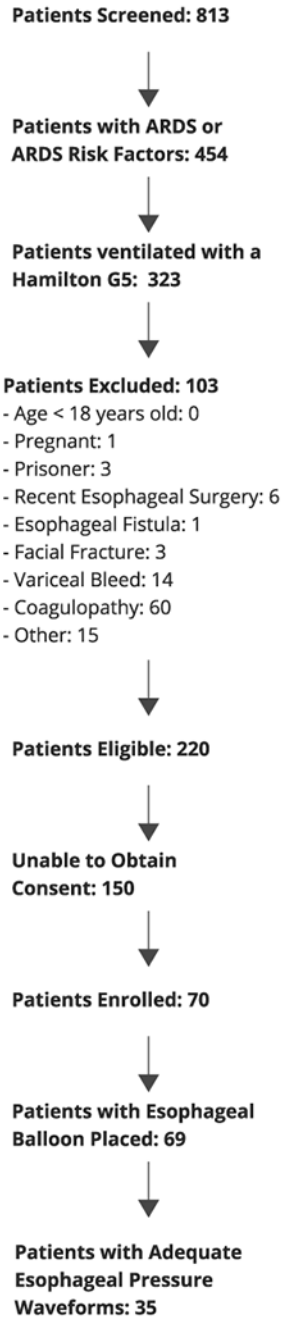

Figure 1:
CONSORT Diagram

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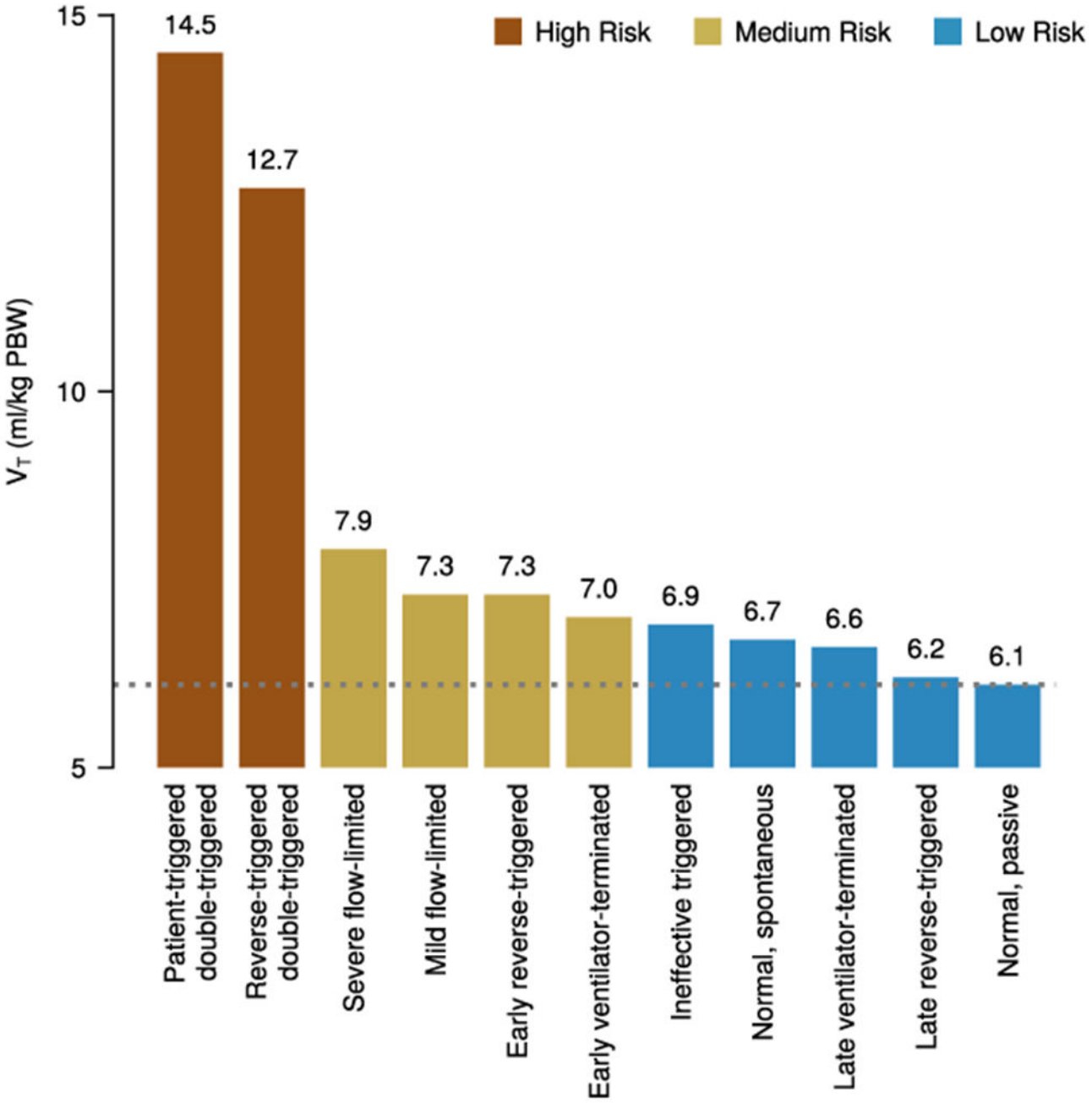

Figure 2:
Predicted Delivered Tidal Volume by Ventilator Dyssynchrony Type

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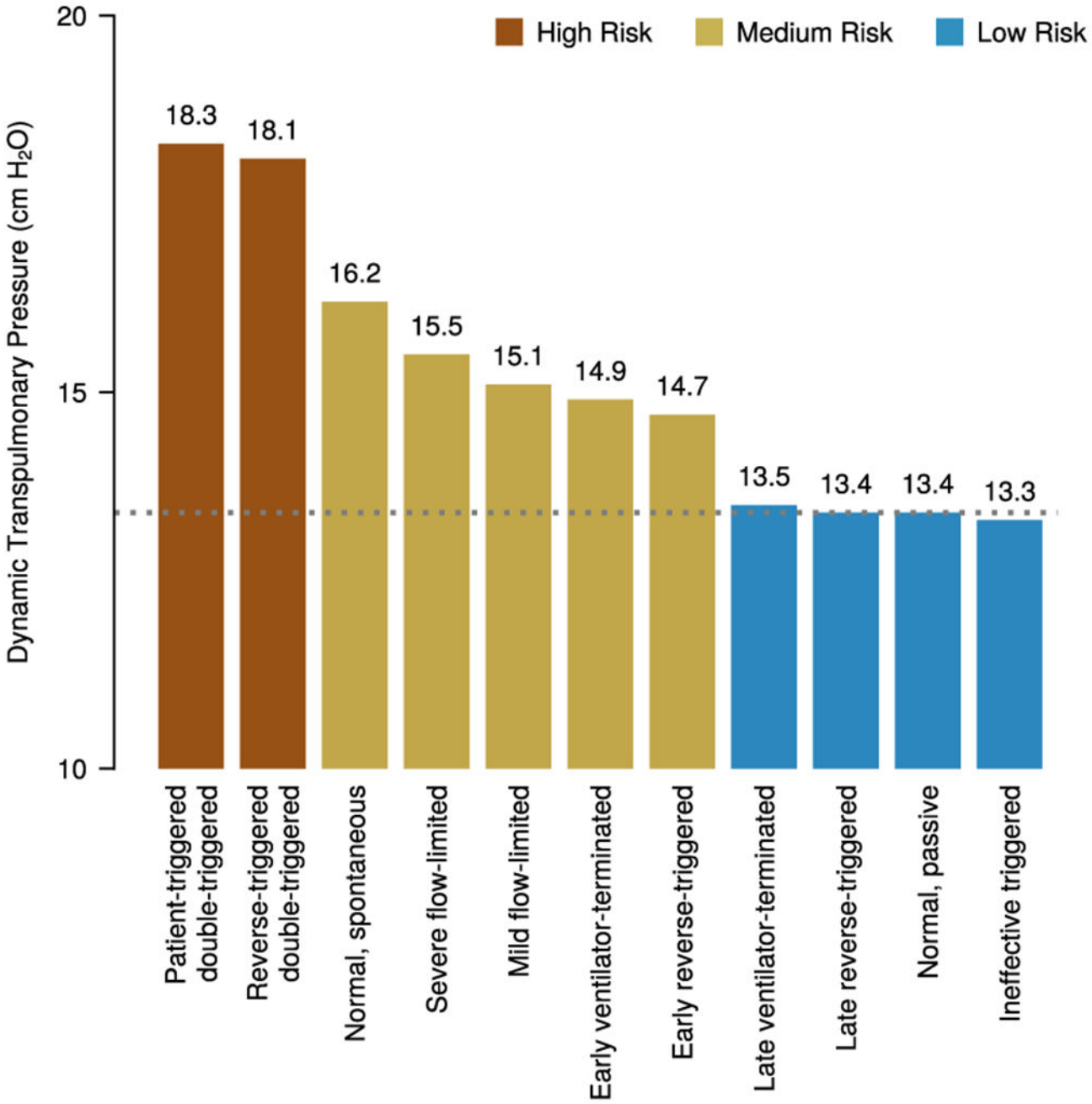

Figure 3:
Predicted Dynamic Transpulmonary Pressure by Ventilator Dyssynchrony Type

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Table 1:

Demographics

Age (mean, std)	54.2±14.8
Female (N, %)	14 (40%)
Caucasian (N, %)	25 (71%)
Initial PF ratio (mean, std)	138.1±69.6
NMB (N, %)	9 (26%)
Mortality (N, %)	
ARDS Risk Factors	
(N, %)	
COVID-19	11 (31%)
Pneumonia	11 (31%)
Sepsis	6 (17%)
Aspiration	2 (6%)
Pancreatitis	2 (6%)
Other	3 (9%)

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Table 2:

Frequency of VD as a percentage of all breaths

VD	N	%
NL	416,560	70.9
NLp	346,250	58.9
NLs	25,853	4.4
RTe	5,599	1.0
RTl	37,370	6.4
DTr	23,949	4.1
DTp	5,132	0.9
FLm	51,631	8.8
FLs	27,313	4.6
EV	12,205	2.1
LVT	1,876	0.3
IE	9,240	1.6

NL: normal breaths, **NLp**: normal passive breath; **NLs**: normal spontaneous breath; **RTe**: early reverse-triggered, **RTl**: late reverse-triggered; **DTr**: reverse-triggered double-triggered; **DTp**: patient-triggered double-triggered; **FLm**: mild flow-limited; **FLs**: severe flow-limited; **LVT**: late ventilator-termination; **EVT**: early ventilator-termination; **IE:** ineffective-triggered